

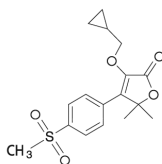
Equioxx[®]

Injection (firocoxib)

Non-steroidal anti-inflammatory drug for intravenous use in horses only.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: EQUIOXX (firocoxib) belongs to the coxib class of non-narcotic, non-steroidal anti-inflammatory drugs (NSAID). Firocoxib is a white crystalline compound described chemically as 3-(cyclopropylmethoxy)-4-(4-(methylsulfonyl)phenyl)-5, 5-dimethylfuranone. The empirical formula is C₁₇H₁₈O₄S, and the molecular weight is 336.4. The structural formula is shown below:



EQUIOXX Injection is a colorless to pale yellow solution. Each mL of EQUIOXX Injection for Horses contains 20 mg of firocoxib as a free base, 550 mg of polyethylene glycol (PEG 400) and 600 mg of glycerol formal.

Indications: EQUIOXX Injection is administered for up to 5 days for the control of pain and inflammation associated with osteoarthritis in horses.

Dosage and Administration: Always provide the Client Information Sheet with the prescription. The recommended dosage of EQUIOXX Injection for intravenous administration in horses is 0.04 mg/lb (0.09 mg/kg) of body weight once daily for up to 5 days. If further treatment is needed, EQUIOXX (firocoxib) Oral Paste for horses can be used at a dosage of 0.045 mg/lb (0.1 mg/kg) body weight for up to an additional 9 days of treatment. The overall duration of treatment with EQUIOXX Injection and EQUIOXX Oral Paste will be dependent on the response observed, but should not exceed 14 days. See EQUIOXX Oral Paste for horses package insert for dosage and administration. EQUIOXX Injection is a non-aqueous solution and should not be mixed with aqueous solutions (Do not flush through intravenous lines using aqueous flush solutions).

Contraindications: Horses with hypersensitivity to firocoxib should not receive EQUIOXX Injection.

Warnings: For intravenous use in horses only. Do not use in horses intended for human consumption.

Human Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental human exposure.

Animal Safety: Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription.

For technical assistance or to report suspected adverse events, call 1-877-217-3543.

Precautions: Horses should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID. Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription. **See Information for Owner or Person Treating Horse** section of this package insert.

Treatment with EQUIOXX should be terminated if signs such as inappetence, colic, abnormal feces, or lethargy are observed.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Horses that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of EQUIOXX Injection with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided.

The concomitant use of protein bound drugs with EQUIOXX Injection for horses has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of firocoxib Injection has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

The safe use of EQUIOXX Injection for horses has not been evaluated in horses less than one year of age, horses used for breeding, or in pregnant or lactating mares.

Consider appropriate washout times when switching from one NSAID to another NSAID or corticosteroid.

Adverse Reactions: The effectiveness of EQUIOXX Injection was established in a biocomparability study demonstrating that EQUIOXX Oral Paste is bioequivalent to EQUIOXX Injection. Thus, additional field studies were not performed to support the effectiveness of EQUIOXX Injection.

In controlled field studies, 127 horses (ages 3 to 37 years) were evaluated for safety when given EQUIOXX[®] (firocoxib) Oral Paste for Horses at a dose of 0.045 mg/lb (0.1 mg/kg) orally once daily for up to 14 days. The following adverse reactions were observed. Horses may have experienced more than one of the observed adverse reactions during the study.

The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a material safety data sheet, please call 1-877-217-3543.

Information for Owner or Person Treating Horse:

You should give a Client Information Sheet to the person treating the horse and advise them of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse reactions may include erosions and ulcers of the gums, tongue, lips and face, weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in some situations, result in death. Clients should be advised to discontinue NSAID therapy and contact their veterinarian immediately if any of these signs of intolerance are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

Adverse Reactions Seen in U.S. Field Studies with EQUIOXX Oral Paste

Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose stool	1	0
Polydipsia	0	1
Urticaria	0	1

EQUIOXX Oral Paste was safely used concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics, during the field studies.

Clinical Pharmacokinetics/ Pharmacodynamics: Based on the comparison data between the intravenous and oral administration, the area under the curve (AUC) for both routes of administration was the same. The average AUC ratio of injectable to the oral product was 103%. The average peak plasma concentration observed one minute following firocoxib intravenous administration was approximately 3.7 fold greater than the observed average peak plasma concentration reached after administration of the oral paste (oral T_{max} = 2.02 hours). The average plasma concentrations following IV injection and oral administration were similar by 2 hours post-dose, after which the concentrations proceeded to decline in parallel. The terminal elimination half-life (T_{1/2} el) values were not significantly different (p>0.05), with values ranging from 14.6 to 68.0 hrs (mean = 31.5 hours) for the oral paste and from 12.6 to 66.3 (mean = 33.0 hours) for the intravenous solution.

The major metabolism mechanism of firocoxib in the horse is decyclopropylmethylation followed by glucuronidation of that metabolite. Based upon radiolabel studies, the majority of firocoxib is eliminated in the urine as the glucuronide conjugate of the decyclopropylmethylated metabolite. Despite a high rate of plasma protein binding (98%), firocoxib exhibits a large volume of distribution (mean Vd (ss) = 1652 mL/kg). The drug accumulation occurs with repeated dose administrations and steady state concentrations are achieved beyond 6-8 daily oral doses in the horse. Dose linearity exists from 1X-2X of 0.1 mg/kg/day after oral administration. Little drug amount distributes into blood cells.

Steady-state plasma firocoxib concentrations at 4 and 24 hours post administration were the same following intravenous or oral administration at each dose in the range of 1X to 5X.

Mode of action: Firocoxib is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity¹ in animal models. Based on *in vitro* horse data, firocoxib is a selective inhibitor of prostaglandin biosynthesis through inhibition of the inducible cyclooxygenase-2 isoenzyme (COX-2)^{2,3}. Firocoxib selectivity for the constitutive isoenzyme, cyclooxygenase-1 (COX-1), is relatively low. However, the clinical significance of these *in vitro* selectivity findings has not been established.

Effectiveness: The effectiveness of EQUIOXX Injection was established in a biocomparability study evaluating EQUIOXX Oral Paste and EQUIOXX Injection. Thus, additional field studies were not performed to support the effectiveness of EQUIOXX Injection. Two hundred fifty-three client-owned horses of various breeds, ranging in age from 2 to 37 years and weighing from 595 to 1638 lbs, were randomly administered EQUIOXX Oral Paste or an active control drug in multi-center field studies. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Horses were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall clinical improvement in a non-inferiority evaluation of EQUIOXX Oral Paste compared to an active control.

At study's end, 84.4% of horses treated with EQUIOXX Oral Paste were judged improved on veterinarians' clinical assessment, and 73.8% were also rated improved by owners. Horses treated with EQUIOXX Oral Paste showed improvement in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was comparable to the active control.

Animal Safety: A target animal safety study was conducted to assess the safety of EQUIOXX Injection followed by EQUIOXX Oral Paste in the horse. Thirty-two clinically healthy adult horses received EQUIOXX Injection intravenously once daily for five days at doses of either 0 mg/kg (control group); 0.09 mg/kg (1X); 0.27 mg/kg (3X); or 0.45 mg/kg (5X the recommended dose). This was followed by once daily oral administration of EQUIOXX Oral paste for nine days at doses of either 0 mg/kg (control group); 0.1 mg/kg (1X); 0.3 mg/kg (3X); or 0.5 mg/kg (5X the recommended dose). This sequence (five days of EQUIOXX Injection followed by nine days EQUIOXX Oral Paste, for a total of 14 days) was repeated three times for a total treatment duration of 42 days (3X the recommended treatment duration of 14 days).

Two male 5X horses demonstrated a white focus in the renal cortex which correlated with tubulointerstitial nephropathy microscopically. The presence of tubulointerstitial nephropathy was considered treatment-related.

One horse from the control group and two horses from the 5X group had injection site swellings during treatment. Injection site changes characterized by inflammatory cell influx and rarely tissue necrosis were seen in all study groups including the control group.

There was a dose-dependent increase in the incidence of oral ulcers and erosions. Elevated hepatic enzymes (GGT or AST) were noted in all study groups at one or more timepoints. One male 5X horse with an elevated GGT value on Day 42 was noted to have tubulointerstitial nephropathy at the time of necropsy. For all horses, these hepatic enzyme elevations generally returned to the reference range by the next time point.

Storage: Store at 20-25°C with excursions between 15-30°C.

How Supplied: EQUIOXX (firocoxib) Injection for Horses will be supplied in sterile, 25 mL amber glass vials for multi-dose use.

¹ McCann ME, Rickes EL, Hora DF, Cunningham PK et al. *In vitro* effects and *In vivo* efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res. 2005 Jul;66 (7):1278-84

² McCann ME, Anderson DR, Bideau C et al. *In vitro* activity and *in vivo* efficacy of a novel COX-2 inhibitor in the horse. Proceedings of the Academy of Veterinary Internal Medicine. 2002. Abstract 114, p.789.

³ Data on file.

Manufactured for:
Merial Limited
Duluth, GA 30096-4640, U.S.A.
1-877-217-3543

Made in Germany

NADA 141-313, Approved by FDA
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